



# Closed-System Transfer Devices For Safe Handling of Injectable Hazardous Drugs

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**W**orker exposure to chemotherapy and other hazardous drugs (HDs) during preparation and administration has been a concern for more than 30 years.<sup>1</sup> Both early and recent studies show workplace and worker contamination, biological marker changes in exposed workers, chromosomal damage in workers, and adverse reproductive events correlated with occupational exposure to chemotherapy, especially the alkylating agents.<sup>2-6</sup>

Guidelines for safer handling of HDs are available from the American Society of Health-System Pharmacists, the Oncology Nursing Society, the Occupational Safety and Health Administration, among others, with most groups advocating engineering controls, personal protective equipment, and safe work practices as the primary methods for reducing worker exposure.<sup>7-9</sup> Closed-system transfer devices (CSTDs) play an increasing role in many health systems as part of an overall approach to reduce occupational exposure to HDs. This review describes the available CSTDs and reviews studies supporting the efficacy of these device.

## Novel Intervention and Initial Studies

A novel intervention developed in Sweden, an HD containment system, or CSTD, called PhaSeal (Carmel



Pharma), received FDA clearance under 510(k) in 1997 as a Class II medical device. A manufacturer-sponsored study done in a Swedish oncology center and published in a US peer-reviewed journal in 1999 demonstrated that the PhaSeal system, which covers pathways of injectable drug transfer during preparation and administration, reduced contamination of workplace surfaces compared with results seen using standard aseptic practices in previously published studies.<sup>10</sup> PhaSeal was used from May 1996 to June 1997, during which time 534 doses (446 g) of fluorouracil (FU) and 132 doses (135 g) of cyclophosphamide (CP) were prepared by 3 experienced nurses mixing on a table top.

Wipe samples were taken one time at 17 spots (15 single, snap-shot wipe samples and 2 blanks) in and around the drug preparation room at the end of the working day, before cleaning. Samples were analyzed

for FU and CP. The authors stated that levels of cytostatic drug contamination after 1 year of use of the PhaSeal system were far lower than those detected following the use of traditional preparation techniques (as reported in other published work at different European locations), but no data on doses or amounts of CP and FU handled in the comparative studies were reported.<sup>10</sup> Although the authors concluded that the results show no detectable levels of environmental contamination from CP or FU in an outpatient clinic following 1 year of use of the PhaSeal system for the preparation and administration of cytostatic drugs, CP was detected in a single-wipe sample taken from the floor in the corridor outside the preparation room. The authors do not address this. Additionally, no statistical evaluation was done of the results of the samples.

A large oncology medical center in the United States undertook an extensive study of PhaSeal that was supported in part by the manufacturer.<sup>11</sup> In a preliminary presentation of this study, Connor et al demonstrated that the PhaSeal device used in conjunction with a biological safety cabinet (BSC) and conventional cleaning procedures, resulted in a 60-fold reduction in surface contamination with ifosfamide (IF) in the BSCs and a 3-fold reduction overall in the pharmacy area, where it was common to handle 19.5 g per day of IF.<sup>11</sup>

In a continuation of their study, Connor et al used the PhaSeal CSTD in a new IV compounding pharmacy, conducting one baseline wipe sampling of 18 areas for FU, CP, and IF.<sup>12</sup> PhaSeal was used to compound the CP and IF, and traditional needle-syringe technique was used for FU. The wipe sampling was repeated once every 4 weeks for 24 weeks, resulting in 6 post-intervention sampling dates. Overall surface contamination was decreased. The authors concluded that a closed-system device, in conjunction with the use of BSCs in an IV admixture area, appeared to contain surface contamination resulting from the preparation of CP and IF. The results of this study led to the adoption of PhaSeal as the norm at the medical center where the study was conducted.

This extensive study demonstrated a number of issues in handling HDs. The remodeled pharmacy retained the same floor and walls, and floor contamination was detected at baseline and persisted throughout much of the study. Cleaning processes were ineffective and resulted in a failure to achieve a true baseline. At the beginning of the study there was low to moderate IF contamination on several locations on the floor; this declined to a very low level by the end of the study. On the final sampling day, a high level of IF was detected in 1 of the 2 BSCs. Although a spill was not documented, the high level may have been the result of improper use or failure of the PhaSeal System, unreported breakage, or contamination by some other means. It should be noted that this study was conducted before the investigation of surface contamination on the outside of drug vials. Subsequent studies show that CP and FU vials are routinely contaminated

when received from manufacturers and distributors.<sup>13</sup>

In another manufacturer-supported study, Wick et al looked at wipe samples of preparation and administration areas and urine samples of 8 staff members (7 active, 1 control) in a newly constructed ambulatory care infusion center and pharmacy facility.<sup>14</sup> Using CP and IF as their marker drugs, the investigators collected 17 wipe samples before implementation (BI) of the PhaSeal system in December 2001 and then collected 21 wipe samples 6 months after implementation (AI). BI, all 17 wipe samples had detectable levels of CP (5 with a CP value above the linear range of the assay) and 11 of the 17 had detectable levels of IF. AI, only 7 wipe samples had detectable levels of CP (none above the range of the assay), and 15 had detectable levels of IF (5 above the range of the assay).

BI, 52 individual urine samples were collected from the 7 subjects and 1 control. Participants provided 24-hour urine samples toward the end of the workweek, when, theoretically, employee exposure would be highest. Thirty milliliters of each urine sample was sent for analysis. Of the 52 samples, 10 had detectable levels of IF. One sample belonged to a technician who worked in the pharmacy but did not prepare chemotherapy drugs. The other 9 samples belonged to a pharmacist who was involved in order entry and checking. The last IF order was processed 3 weeks before these urine collections. Eighteen urine samples had detectable levels of CP. One nurse had a positive sample, a second nurse had 3 positive samples, 1 pharmacy technician had 8 positive samples, and each pharmacist had 3 positive samples.

AI, 54 urine samples were collected from the same 8 participants. All samples were below detectable limits of IF and CP. The authors said that the 5 employees who had detectable levels BI could have been exposed in numerous ways, including handling vials or touching previously contaminated surfaces. Additionally, although AI surface contamination decreased for CP but increased for IF, both agents were not detectable in the second set of urine samples. The authors offer no explanation as to the apparent discrepancy between handling activities of CP and IF and the uptake of drug in the workers. The authors conclude that the PhaSeal system appeared to reduce surface contamination with and exposure of health care personnel to CP and IF.

In the discussion of their study, the authors noted that unlike a BSC, which represents a one-time capital expenditure that can be depreciated, PhaSeal creates an added annual expense. Depending on configuration and order volume, this system may add \$6 to \$15 to the cost of each chemotherapy drug infusion. During this study, the authors purchased the PhaSeal system at a price negotiated by their group purchasing organization. They estimated that the system would add approximately \$300,000 in annual expenses if deployed fully across their entire hospital system. It is possible to add the cost of the system to the cost of

the chemotherapy drug infusion, but reimbursement will vary according to payer mix. The authors also stated, "Our most compelling reason for implementing the PhaSeal system was our ethical responsibility to safeguard our employees. Our study demonstrated a potential health risk, as well as identified a tool that appears to reduce that risk."

These early studies suggested that CSTDs helped to contribute to reduction of surface contamination and employee exposure to HDs. It must be remembered that good compounding techniques and robust cleaning procedures also are important factors that mitigate outside sources of contamination.

### NIOSH Alert and CSTDs

In 2000, The National Institute for Occupational Safety and Health (NIOSH) assembled a team to review new studies and update recommendations for HD safe handling practices. This resulted in the 2004 Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings.<sup>15</sup> After reviewing the intervention studies, NIOSH included a section on closed systems in the Alert.

In the 2004 Alert, NIOSH defines a "closed system" as a device that does not exchange unfiltered air or contaminants with the adjacent environment. It further defines a "closed-system drug-transfer device" for use in compounding and administering sterile doses of chemotherapy and other HDs, as a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of HD or vapor concentrations outside the system. From this definition, the term and concept of CSTD were developed, although the acronym, CSTD, is not used in the Alert. Based on the studies published up to that time, the authors of the Alert noted that "Evidence documents a decrease in drug contaminants inside a Class II BSC when a closed-system transfer device is used" and concluded that facilities should "consider using devices such as closed-system transfer devices, glovebags, and needleless systems when transferring [HDs] from primary packaging (such as vials) to dosing equipment (such as infusion bags, bottles, or pumps)."<sup>15</sup>

The NIOSH definitions of the 2 terms (*closed system* and *closed-system drug-transfer device*) are descriptive but do not include a performance standard. To adequately assess a CSTD, there should be a performance standard that would establish the test methods and criteria for successfully meeting the standard. Similar to the ASTM standard on chemotherapy gloves,<sup>16</sup> specific drugs or surrogates, predetermined drug amounts and concentrations, exposure time, and acceptable containment limits are needed to determine if a CSTD system is effective. Although absolute containment is ideal, it is unlikely and, as in radiation safety, ALARA (As Low As Reasonably Achievable) should be acceptable.

In the absence of a performance standard, researchers



In traditional compounding with needles and syringes, leakage has been shown as both powder and liquid aerosols around the drug vial septum, the disengaged needles, and the point of injection into the IV bag. In traditional administration with open IV bag ports, IV set spikes, and Y-site connections, leakage has been shown during preparation for administration (spiking and priming the IV bag) and during disengagement of chemo IV sets from patients.

A CSTD should cover the following steps in the compounding and administration process during which the drug has been shown to be released into the environment during manipulation, ie, when:

- Injecting the syringe/needle into vial through septum
- Disengaging syringe/needle from vial septum
- Injecting syringe/needle into IV bag
- Spiking the IV bag by placing an IV set into a bag containing drug
- Priming the IV set to remove air before attaching to patient access
- Administering an IV push dose from a syringe into a Y-site of IV tubing
- Disengaging secondary sets or push connections from primary set or from patient

### Figure. How should a CSTD work?

have proposed a number of methods and surrogates to assess the effectiveness of various devices marketed as closed systems (Figure, Table 1).<sup>10,12,14,17-29</sup> For example, a series of studies from Sweden have used radioactive technetium to evaluate different types of closed systems, finding both diaphragm and filtered systems to be fairly equivalent with respect to containment.<sup>17,18,29</sup> In one of these studies, the authors noted, however, that "the tested system (filtered) in this paper cannot physically be regarded as a closed system according to the National Institute for Occupational Safety and Health definition of closed system (NIOSH, 2004), since air can

pass in and out of the system during preparation.”<sup>18</sup> The authors subsequently reversed their position after conferring with NIOSH.<sup>30</sup> In a letter to the editors of the journal, the authors quote a NIOSH statement that: “the Alert’s glossary was not really intended to be a specification guide for equipment design criteria. Rather, we sought to identify the desired function that the defined piece of equipment should provide. In the case of the CSTD, the intended function was to preserve the sterility of the product while preventing the escape of a [HD], in whatever form it may exist, into the surrounding environment. In that regard, if a hypothetical CSTD was successful in meeting these performance criteria during the drug transfers for which it was intended, we (NIOSH) would probably consider it as meeting the definition. If however, the [HD] under manipulation included a vapor component or could change phase to vapor during the drug transfer process, leading to escape of drug from the system, then that system would fail to meet the intended function of our definition.”<sup>30</sup>

The FDA recently created a new Class II Device Product Code, ONB, with the description “Closed Antineoplastic and Hazardous Drug Reconstitution and Transfer System.”<sup>31</sup> This product code has no performance standard or specification guide. It does, however, specify “antineoplastic and other hazardous drugs” in the definition, possibly limiting the surrogates that may be used to evaluate such devices.

There are a number of FDA-cleared Class II medical devices that are marketed as “CSTDs” or other “closed” or “contained” systems available from various manufacturers. They differ in how they attempt to meet the NIOSH definition of a closed-system drug-transfer device (Table 2).<sup>15</sup> For the remainder of this article, CSTD will be used to describe a generic Class II medical device marketed for the purpose of safe handling of HDs. The following describes the available FDA-cleared Class II medical devices generically termed CSTDs.

PhaSeal is a proprietary system of a vial device (Protector) that uses a locking cap with a small spike to secure access to a vial. The Protector uses a diaphragm to contain the air from the vial and any liquid, powder, or gaseous aerosol generated in reconstitution or transfer. An Injector attaches to a syringe and accesses the Protector with a unique locking system. Once locked, the Injector passes a cannula through the Protector spike into the vial through a double membrane. The diaphragm expands and contracts to handle the air from the syringe and vial. PhaSeal has an Infusion Adapter that allows a closed connection between the drug in a syringe and an IV bag and a dry connection to the spike of any IV set. PhaSeal also provides an adapter for the syringe into a Y-site for IV-push administration.

ChemoClave Genie and Spiros by ICU Medical uses a closed male luer (Spiros) that attaches to Clave connectors to allow needle-free access to HD vials and IV sets. The Genie is a vial-access device that uses an expandable balloon inside the vial to equalize vial pressure when liquid drug is withdrawn. The Genie is equipped

with a needle-free Clave connector. ICU Medical has a selection of IV devices with Clave connectors that facilitate transfer of drug through syringes using the Spiros. These devices provide a system for access to the IV bag, IV sets, and Y-sites for various administration techniques. ICU Medical also provides several vented vial-access spikes with hydrophobic filters that fit various sizes of vials.

OnGuard by B. Braun uses Tevadaptor components to provide a “contained medication system.” The 2 primary components are the Tevadaptor Vial Adaptor and Tevadaptor Syringe Adaptor. The vial adaptor contains an activated charcoal drug-binding matrix and a hydrophobic 0.2-micron sterilizing-grade membrane to contain HD aerosols. All system components use elastomeric seals to prevent fluid escape and provide audible and tactile confirmation of secure connections. OnGuard has devices that address compounding and administration via needle-safe connectors. OnGuard provides a bag-access device, IV push adapters, and IV sets that are compatible with its system components.

Texium by Care Fusion is a closed male luer designed to partner with the SmartSite needle-free valve to deliver a closed system for compounding and administration of HD doses. The SmartSite Vented Vial Access Device uses a 0.2-micron hydrophobic air-venting filter to equilibrate air pressure in HD vials during compounding. The SmartSite Add-On Bag Access Device allows the Texium to connect to an IV bag to add drug and provides a dry connection for spiking an administration set into the IV bag. The Texium male luer connects to any SmartSite valve for various administration techniques.

Equashield by Equashield Medical uses a proprietary syringe unit with 2 chambers—a liquid chamber and an air chamber—located at the end of the syringe piston. A dual-needle air-to-liquid exchange system communicates between chambers displacing liquid from the vial with equivalent air from the air chamber. Equashield maintains constant equal pressure inside the vial to prevent the escape of vapors and aerosols. Equashield uses tight seal double-membrane connectors between its system components—the vial and syringe adapters and the bag and IV-push adapters. Equashield has fixed fully shielded needles to prevent accidental sticks.

## Assessing a CSTD

In the absence of a performance standard, some CSTDs have been evaluated in published studies, many in peer-reviewed publications. Some manufacturers have chosen to use contracted laboratories to assess the effectiveness of their devices in a limited setting with a selected protocol. Studies have been done in clinical environments and in controlled laboratories. Some studies use surface wipe sampling of marker drugs to assess HD residue, whereas others have used surrogates including fluorescein, titanium tetrachloride, and radioactive technetium to assess the containment properties of CSTDs. Each method has had some success

in providing insight into how and how well different CSTDs function, but no method has been adopted as determining criteria for workplace or worker safety for the CSTDs (ie, a performance standard).

In reviewing the literature and available information on CSTDs, the preponderance of studies has been done with PhaSeal, the first of the new generation of protective devices to clear the FDA's 510(k) process. Carmel Pharma increased awareness of the issue of workplace contamination with HD residue by sponsoring wipe-sampling studies in clinical settings. Two major studies were described in the section on Novel Intervention and Initial Studies.<sup>12,14</sup> Two more-recent publications chronicle sponsored wipe samplings before and after PhaSeal implementation, the first group describing evaluations from June 2000 to May 2005 at 22 US hospital pharmacies and the second describing evaluations from August 2004 to November 2010 at 30 US hospital pharmacies.<sup>19,20</sup>

### Clinical Studies and Wipe Sampling

CSTD studies often are referred to as "clinical" because they are done in a clinical setting with real drug doses that will be administered to patients. These studies use wipe sampling of specific "marker" drugs to evaluate surface contamination. Some of these studies examine both the preparation and administration areas for levels of surface contamination before and after intervention. Although clinical studies offer a perspective on the overall degree of HD surface contamination found in actual working facilities, they have limitations in assessing interventions as specific as CSTDs.<sup>2,12,14</sup> Most clinical studies do not control for outside sources of contamination, for example, the drug residue found on the outside of many drug vials. They rarely control or report cleaning activities and when cleaning is done in relation to sampling or if the cleaning procedures are effective in removing the marker HD.<sup>12,14</sup> Clinical studies often are affected by spills that may not be related to the CSTD but affect the overall level of surface contamination.<sup>12</sup> These studies also are affected by using a "snap-shot" technique, taking wipe samples at a single time (a "snap shot") during a compounding and/or administration period that may extend for weeks. One of the most difficult variables to control in a clinical study is how much drug was actually handled before sampling. Most clinical studies do not even attempt to identify specific drug quantities, generally providing an "average" amount of the marker drugs used in a given time period. In wipe-sampling studies, there are variations in the number of wipe samples taken, the range of sizes of the area to be sampled, the amount of solvent used to sample the desired space, the recovery of the drug from a given surface material using a specific solvent, the people who do the wipe sampling, and the period of time studied. The technique for wiping and the force exerted also affect the recovery of marker drug from surfaces. Many of the studies have a

small number of samples and most have no statistical significance. Overall, clinical studies evaluating CSTDs have not demonstrated a direct correlation of drugs handled to surface contamination measured.

### PHASEAL STUDIES

Harrison et al conducted a detailed and comprehensive study.<sup>21</sup> Using an educational grant from Carmel Pharma, the authors designed a multisite, clinical, wipe-sampling study to compare surface contamination with FU and CP in a 3-phase study. Phase 1 was before the use of PhaSeal; phase 2 was during use of PhaSeal; and phase 3 was after PhaSeal was removed from all 3 sites. During the 36-week study, 18 time points and 342 samples ensured sufficient data for statistical analysis. All operators were well trained in the new system. Cleaning methods and times were controlled, as was spill reporting, and spill cleanup protocols were in place. CP and FU were reported as mean amount of drugs prepared per 2-week sampling period per site. All data were normalized per total grams of CP prepared during each 2-week sampling period. Precleaning or wipe sampling of CP and FU vials was not reported. Post-test multiple comparisons showed surface contamination with CSTD use (phase 2) to be significantly less than without CSTD use (phase 1,  $P<0.001$ ; phase 3,  $P<0.001$ ). The median surface contamination showed statistically significant differences across the 3 phases for each site (site A:  $P=0.0164$ ; site B:  $P=0.0458$ ; site C,  $P<0.0001$ ). Contamination in the CSTD phase was less than in the control phases, but the differences did not reach statistical significance ( $P>0.05$ , Dunn test) for sites A and B. The authors noted that the levels of contamination detected before CSTD use for 2 sites were much lower than they anticipated and generally less than reported in the literature to date. They concluded that the use of a CSTD in the BSC in conjunction with standard HD preparation techniques significantly reduced CP surface contamination compared with standard techniques alone.

In a 24-month cross-sectional study supported by Mayne and Carmel Pharma, Tans et al looked at surface and glove contamination of FU, CP, and IF in different periods with and without PhaSeal.<sup>22</sup> They did not find the PhaSeal system effective in reducing surface contamination, but their results may have been influenced by a big spill due to an incorrect use of PhaSeal. There was an improvement in glove contamination with the use of the PhaSeal system.

In the 2 previously mentioned studies chronicling wipe samples and use of PhaSeal, the ratio of "spot wipes" to facilities is very low.<sup>19,20</sup> In the study of 22 US hospital pharmacies, the authors reported 114 samples per 22 sites where the surface areas wiped ranged from 300 to 11,050 cm<sup>2</sup>. Statistical analysis is reported for the composite results.<sup>19</sup> Although 68% of the wipe samples of the 4 surfaces tested positive for CP with the CSTD in use, compared with the standard

*Text continues on page 8*

**Table 1. CSTD Intervention Studies With Marker Drugs Or Measurable Surrogates**

Citation	Study Type/ Methodology	Intervention	Comparison	Results	Sponsor	Comments
Sessink <i>Hosp Pharm</i> 1999 <sup>10</sup>	Clinical/not controlled; CP, FU; snapshot single wipe sample taken once over 1 y, 17 spots	PhaSeal	Published studies	Reduced HD surface contamination compared with published reports	Financial support by Carmel Pharma	No PEC in use; no BI wipes
Connor <i>AJHP</i> 2002 <sup>12</sup>	Clinical/not controlled; CP, IF, FU; snap-shot wipe samples at baseline (18 spots), then every 4 wk for 24 wk (6 AI sampling dates)	PhaSeal for CP, IF	Needle syringe for FU	PhaSeal appeared to contain surface contamination resulting from preparation of CP and IF when used with a BSC in a high-volume IV admixture area	Partial support by Carmel Pharma	Vial residue not considered; cleaning appears ineffective; “true” baseline not achieved with cleaning and sampling, although levels decreased over time
Nygren <i>J Environ Monit</i> 2002 <sup>17</sup>	Laboratory setting; simulated preparation and administration of radioactive <sup>99m</sup> Tc and platinum standard; surface contamination measured by radioactive leakage of <sup>99m</sup> Tc and air sampling with platinum for emissions; 10 nurses simulated 6 preparations and administrations (6 mL of radioactive solution in 10-mL syringes)	PhaSeal	Traditional technique	Difference in airborne emission was small and NS, although no statistical analysis was done; all subjects had leakage in preparation and administration using open technique, but it varied; leakage was consistently less using the closed system, which showed 3-4 times lower volumes for all measurements	Support by the Swedish Council for Working Life and Social Research	Studies with radioactive tracers use small volumes of tracer manipulated with small syringes; this does not appear to be a good surrogate for HD doses that are generally large and require large syringes to prepare and administer; larger volumes are more difficult to manipulate
Wick <i>AJHP</i> 2003 <sup>14</sup>	Clinical/not controlled; CP, IF; snap-shot wipe and urine sampling; BI: wipe samples from 17 spots and 52 urine samples; AI: 21 samples as a single snap shot once and 54 urine samples	PhaSeal	BI and AI in same setting after 6 mo	<i>Wipe samples</i> BI: 17/17 detectable levels of CP; 11/17 detectable levels of IF AI: 7/21 detectable levels of CP; 15/21 detectable levels of IF, with 5/15 over range of assay <i>Urine samples</i> BI: 10/52 detectable levels of IF, 18/52 detectable levels of CP AI: All samples were below limits of detection for CP and IF	Support by Carmel Pharma	Authors noted some deficiencies in the study and concluded that PhaSeal appeared to reduce employee exposure to and surface contamination with CP and IF; they elected to implement PhaSeal in all of their compounding and administration sites, despite a significant cost increase

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Tans <i>J Oncol Pharm Pract</i> 2004 <sup>22</sup>	Clinical/not controlled; CP, FU, IF; surface and glove contamination over 24 mo in different segments with and without intervention; 104 spot samples taken BI and 4 times AI	PhaSeal	BI and AI in same setting	Authors note intervention did not show a clear difference in reduction in surface residue, possibly due to a big spill caused by an incorrect use of the system; improvement noted in glove contamination with PhaSeal	Support by Mayne and Carmel Pharma	Only the results of glove tests were interesting to the authors due to higher levels of contamination, so changes were made to increase glove testing
Harrison <i>AJHP</i> 2006 <sup>21</sup>	Clinical/ controlled for cleaning and spills; CP, FU; wipe sampling cross-sectional study done in 3 phases (control/ CSTD/control) in 3 sites; 36-wk study, 18 snap-shot time points, and 342 samples	PhaSeal	BI and AI in each site compared with standard preparation techniques	324/342 wipes positive for CP; median surface contamination significantly different across 3 phases ( $P<0.00001$ ), consistent across sites; CSTD in BSC with standard HD technique reduced CP residue compared with standard techniques alone; no conclusive result for CSTD for FU outside of BSC	Support by unrestricted educational grant from Carmel Pharma	FU prepared on countertop, not in PEC
Nygren <i>Ann Occup Hyg</i> 2008 <sup>18</sup>	Laboratory setting; simulated preparation of radioactive <sup>99m</sup> Tc; 8 pharmacists made 75 test preparations in BSC; 6 mL of diluted <sup>99m</sup> Tc was manipulated to simulate preparation; bench covers and gloves were collected for radiation assessment as a measure of leakage	Tevadaptor (marketed in the United States as OnGuard with Tevadaptor components)	Leakage compared with results of previous studies	Leakage was <100 nL for all 75 preparations and <1 nL for 70 preparations; biggest spill during a single preparation was 53.8 nL; showed Tevadaptor drug-handling system has performance similar to drug-handling systems regarded as closed systems	Manufacturers of the device paid the hospital pharmacy at the University Hospital of Northern Sweden for the tests	Authors refer to a Swedish Pharmacy (Apoteket AB) Internal Quality Manual that prescribes a limit value of 100 nL total spill volume on bench cover and gloves for 1 preparation; this appears to be performance standard for Sweden; studies with radioactive tracers use small volumes of tracer manipulated with small syringes
Ledford <i>HOPA</i> 2010 <sup>23</sup>	Clinical/not controlled; CP, FU, MTX; wipe sampling; each system assessed along with routine decontamination using SurfaceSafe and standard techniques in the same clinical setting for 14 d	PhaSeal compared with ICU Medical CSTD (exact components not reported)	Surface contamination measured by wipe sampling for 14-d period with each intervention	Authors concluded that the products generally are equivalent and resulted in un-detectable levels of CP, FU, and MTX ( $P=0.08-0.14$ )	Funding not disclosed	In treatment areas, terminal PhaSeal Injector was not consistently used, but the complete ICU Medical system was used and contributed to 70% lower levels of exposure to the HDs analyzed

AI, after implementation; BI, before implementation; BSC, biological safety cabinet; CP, cyclophosphamide; FU, 5-fluorouracil; HD, hazardous drug; IF, ifosfamide; MTX, methotrexate; NS, not statistically significant; PEC, primary engineering control; SA, surface area; SD, standard deviation; <sup>99m</sup>Tc, technetium 99m

Based on references 10, 12, 14, 17-29.

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**Table 1. CSTD Intervention Studies With Marker Drugs Or Measurable Surrogates** (continued)

Citation	Study Type/ Methodology	Intervention	Comparison	Results	Sponsor	Comments
Zock <i>J Oncol Pharm Pract</i> 2011 <sup>24</sup>	Laboratory setting; controlled for amounts of drug, cleaning, specific manipulations; simulated preparation of CP doses; wipe samples of vials, surfaces of BSC, floor and preparer's gloves; 22 wipe samples and 5 field blanks for both phases	PhaSeal and ChemoClave (Genie/Spiros)	Wipe sampling of marker drug CP, with identical protocols for each intervention	<i>After ChemoClave:</i> no CP detected on BSC airfoil/grill or floor; CP was detected on BSC workbench and 1 pair of gloves <i>After PhaSeal:</i> CP detected on the BSC workbench, but not on BSC airfoil/grill, floor, or gloves	Support by ICU Medical	Authors concluded that small number of samples precluded statistical analysis; of 20 g CP reconstituted, only 6 g were actually transferred using small increments and syringes
Sessink <i>J Oncol Pharm Pract</i> 2011 <sup>19</sup>	Clinical/not controlled; CP, IF, FU; snap-shot wipe sampling taken once BI and AI at each of 22 US hospital sites, 114 wipes/22 sites (about 2 samples per site BI and AI)	PhaSeal	BI and AI in same setting compared with the standard preparation techniques	AI: composite results show significant reduction in levels of contamination for all drugs (CP: $P<0.0001$ ; IF: $P<0.001$ ; FU: $P<0.01$ )	Financial support provided by Carmel Pharma	Individual site samples too small for statistical analysis; variables include range of SA wiped (300 to 11,050 cm <sup>2</sup> ) and each site performed own wipe samples
LeGarlantezec <i>Ann Pharm Fr</i> 2011 <sup>27</sup>	Laboratory setting simulated preparation of <sup>99m</sup> Tc (modification of Nygren <sup>18,19</sup> ); evaluation criteria included transfer performance of the radioactive solution from one vial to another, measuring leakage, contamination, dead space, residual volume, and efficiency	PhaSeal with expansion chamber; Tevadaptor with filter; ChemoClave with filter and Spiros; Smart-site with filter and Texium	Weighted ratings for transfer performance of solution from vial to vial; leakage of device; ease of use; operator preference considered	Teva and CareFusion devices seemed more efficient with ability to transfer solutions with low dead volume and low-level contamination around manipulation area; PhaSeal scored poorest in efficiency and user preference but high in containment	No sponsor disclosed	Training was not addressed and filtered systems are more intuitive to use; studies with radioactive tracers use small volumes of tracer manipulated with small syringes

Text continued from page 5

preparation techniques, a significant reduction in levels of contamination was observed for all drugs (CP:  $P<0.0001$ ; IF:  $P<0.001$ ; FU:  $P<0.01$ ).

The study of 30 US hospital pharmacies yielded 143 samples or approximately 2 wipes per site before and after intervention.<sup>20</sup> The statistical analysis again is based on the composite with a significant reduction in levels of contamination being observed for all surfaces after the CSTD compared with standard preparation techniques ( $P<0.0001$ ). In this second study, 80% of the wipe samples of the 4 surfaces tested positive for CP contamination with use of the CSTD.

#### STUDIES OF OTHER CSTDS

A Florida medical center presented a wipe-sampling study sequentially comparing PhaSeal and the

ICU Medical CSTD (exact components not reported) for contamination during preparation and administration of FU, CP, methotrexate (MTX), and platinum agents.<sup>23</sup> Each system was assessed along with routine decontamination using Surface Safe and standard techniques in the same clinical setting for 14 days. In the pharmacy, both CSTDs provided equivalent control of surface contamination when used in combination with daily cleaning treatment. In the treatment areas, the terminal PhaSeal Injector was not consistently used, but the complete ICU Medical system was used and contributed to 70% lower levels of exposure to the HDs analyzed in the study. The authors concluded that the products are generally equivalent and resulted in non-detectable levels of FU, CP, and MTX ( $P=0.08-0.14$ ). As in most clinical wipe-sampling studies, the amounts of drug handled were not reported. The assumption is that



**Table 1. CSTD Intervention Studies With Marker Drugs Or Measurable Surrogates**

Citation	Study Type/ Methodology	Intervention	Comparison	Results	Sponsor	Comments
Clark <i>J Oncol Pharm Pract</i> 2013 <sup>26</sup>	Clinical/not controlled; CP, FU; wipe sampling of 12 locations as 3 snap shots: with existing methods and no cleaning, after thorough cleaning and 2 mo AI, and 12 mo AI (Equashield); areas peripheral to compounding BSC were wiped	Chemo Dispensing Pin and Equashield	Existing technique of Chemo Pin compared with CSTD (Equashield) intervention	The results of first 2 sets of wipe samples showed contamination with CP on about half of the positions in all departments during both collection periods, but levels of contamination were very low (most just above the detection limit); results from final collection period showed no contamination with CP or FU in the pharmacy, infusion suite or offices of the cancer center	No specific grant from any funding agency in the public, commercial, or not-for-profit sectors	The authors concluded that use of CSTDs for preparing and administering chemotherapy <i>eliminated</i> surface contamination with cytotoxic agents at ambulatory chemotherapy infusion center; this appears overstated because many factors affect surface contamination in a year-long period that could not be determined by a single snap shot of 12 wipe samples
De Ausen <i>AJHP</i> 2013 <sup>28</sup>	<sup>99m</sup> Tc in form of sodium pertechnetate; 15 wipe samples performed by each of 9 participants for sample size of 135 per system; syringe and vial adapters were connected and 6 mL of the test solution were drawn into syringe; then vials and syringe adapters were disconnected and wipe sampling was done on the syringe adapters and their paired spiked vial adapters at usual point of entry	ChemoClave with Genie and Spiros; OnGuard Contained Medication System with Tevadaptor components; and PhaSeal	Leakage measured by radioactivity detected on swabs was compared among all systems	Significant difference in control radioactivity detected, with ChemoClave having a higher mean than both PhaSeal and OnGuard; differences seen in leakage among devices, with PhaSeal having lowest geometric mean leakage, followed by OnGuard and ChemoClave; mean leak volume varied significantly among participants	Funded by the Department of Pharmacy, Tripler Army Medical Center	Study limited to leak volumes on CSTD connection between the syringe and vial; wiping methodology requires touching the membrane connections; PhaSeal has most recessed membrane of the vial access devices, so it is the most difficult to reach, possibly affecting the results; common comment from participants was that it was more difficult to learn how to use PhaSeal than the other devices
Sessink <i>Hosp Pharm</i> 2013 <sup>20</sup>	Clinical/not controlled; CP; snap-shot wipe sampling taken once BI and AI at each of 30 US hospital sites, 143 samples/30 sites	PhaSeal	BI and AI in same setting compared with the standard preparation techniques; results compared with previous study <sup>22</sup>	AI: analysis of composite results showed significant reduction in levels of contamination ( $P<0.0001$ ); 80% of the wipe samples of the 4 surfaces were positive for CP contamination with CSTD, but levels of CP recovered were lower	Financial support provided by Carmel Pharma	Individual site samples too small for statistical analysis; results of this and 2010 study are identical

AI, after implementation; BI, before implementation; BSC, biological safety cabinet; CP, cyclophosphamide; FU, 5-fluorouracil; HD, hazardous drug; IF, ifosfamide; MTX, methotrexate; NS, not statistically significant; PEC, primary engineering control; SA, surface area; SD, standard deviation; <sup>99m</sup>Tc, technetium 99m

Based on references 10, 12, 14, 17-29.

Table continues on next page

**Table 1. CSTD Intervention Studies With Marker Drugs Or Measurable Surrogates** *(continued)*

Citation	Study Type/ Methodology	Intervention	Comparison	Results	Sponsor	Comments
Sewell EAHP 2013	Laboratory wipe-sampling study of 5 marker drugs (cisplatin, oxaliplatin, and carboplatin—all assayed as platinum—and epirubicin and FU); surface wipe samples, used gloves and preparation pads were collected for analysis; surfaces of filled syringes and infusion bags also sampled	Tevadaptor (marketed in US as OnGuard with Tevadaptor components)	Compared with standard needle and syringe technique (BI)	BI: all sampled surfaces (including surfaces of filled syringes and infusion bags) contaminated with marker drugs AI: isolator surfaces were below limits of detection of assays; and contamination on gloves, preparation mats, and surface of infusion containers was markedly lower than at baseline	Support by Teva	Researcher concluded that Tevadaptor reduced both the frequency and amount of surface contamination by the marker drugs when used in similar quantities BI

AI, after implementation; BI, before implementation; BSC, biological safety cabinet; CP, cyclophosphamide; FU, 5-fluorouracil; HD, hazardous drug; IF, ifosfamide; MTX, methotrexate; NS, not statistically significant; PEC, primary engineering control; SA, surface area; SD, standard deviation; <sup>99m</sup>Tc, technetium 99m

Based on references 10, 12, 14, 17, 22-29.

during each 2-week period, the drugs handled in the clinical setting would be similar for each CSTD. Sponsorship of the study was not disclosed.






In a simulation study supported by ICU Medical, Zock et al used wipe sampling of CP in a controlled environment with a specific handling protocol to compare PhaSeal and the ICU Medical ChemoCLAVE closed system using the Genie and Spiros.<sup>24</sup> They used an experimental laboratory setting with a Class 100 clean room and a Class II BSC vented to the outdoors for all procedures. One technician with 7 years of experience with PhaSeal and more than 1 year using the ICU Medical devices performed the dilutions and transfers to syringes and IV bags. Attempts were made to control, minimize, and evaluate other known sources of environmental contamination including precleaning work-area surfaces that would be wipe-sampled as well as wipe-sampling CP 1-g vials before mixing. All wipe sampling was done using Cyto Wipe Kits (Exposure Control B.V.) and samples were stored and shipped to Exposure Control and assayed using previously validated recovery and analytical methods.

Two separate trials simulating HD compounding of CP in a specific protocol were performed with the 2 different closed-system products. After cleaning and before compounding CP, 3 wipe samples of specific work surfaces were done before each intervention, and all samples were below the limit of detection. Composite wipe sampling was done of the 40 CP 1-g vials used for the study. Two wipe samples of vials used in the ChemoCLAVE trial were above the level of detection. The remaining vial wipes were below detection.

Low levels of CP were detected on the BSC workbench surface following both trials. The authors noted that based on the limited number of samples obtained during this preliminary study (12) and the determination of the presence of the CP on the drug vials, no statistical evaluation was performed to compare the relative effectiveness of the 2 systems tested and that further study and statistical analyses are needed. In this protocol, only 6 g of the 20 g of CP were actively transferred for each phase of the study, so more than two-thirds of the drug was discarded. In actual practice, the volumes of transfer would be greater and the time involved probably much smaller.

Sewell presented a wipe-sampling study of 5 marker drugs prepared in a negative-pressure pharmaceutical isolator in the UK's University of Plymouth Aseptic Laboratory.<sup>25</sup> The initial preparation of epirubicin, FU, cisplatin, oxaliplatin, and carboplatin (the latter three assayed only as platinum) was done with conventional syringe and needle technique. This was then compared with the surface contamination obtained over a second period of preparation using a Tevadaptor device (similar to the US CSTD OnGuard with Tevadaptor components). Wipe samples were taken for 1 week (baseline period) from predefined areas in the isolator and from the surfaces of IV infusion bags and prefilled syringes. Gloves and preparation mats used during this period also were collected and analyzed. Following a 1-week training period, the Tevadaptor was introduced and wipe sampling of the same surfaces and collection of consumables was continued for a further week (intervention period). All samples were analyzed using

**Table 2. Available CSTDs**

Device(s)	Company	Components	Website (s)
CareFusion Closed-system solution: Texium closed male luer and SmartSite needle-free valve products	CareFusion 	Filtered drug vial adapter—SmartSite needle-free valve and vented vial-access device; Needle-free syringe adapter-Texium closed male luer; SmartSite add-on bag-access device; needle-free primary and secondary sets help achieve a closed system during administration of HDs when partnered with the Texium closed male luer.	<a href="http://www.carefusion.com/medical-products/infusion/iv-sets-accessories/texium.aspx">http://www.carefusion.com/medical-products/infusion/iv-sets-accessories/texium.aspx</a> <a href="http://www.carefusion.com/medical-products/infusion/iv-sets-accessories/SmartSite.aspx">http://www.carefusion.com/medical-products/infusion/iv-sets-accessories/SmartSite.aspx</a> <a href="http://www.carefusion.com/pdf/infusion/closed_system_solution_brochure.pdf">www.carefusion.com/pdf/infusion/closed_system_solution_brochure.pdf</a>
BD PhaSeal CSTD	Carmel Pharma, BD Medical 	Drug vial adapter with expanding diaphragm for containment (Protector); Needle-Safe syringe adapter (injector) that advances and retracts metal needles when it is locked into connection device; Infusion adapter add-on bag-access device; IV push adapter (connector) attaches to the patient's IV line to connect to the injector; long design may be used with needle-free ports. Selection of IV infusion sets with PhaSeal connectors.	<a href="http://www.carmelpharma.com">www.carmelpharma.com</a> <a href="http://www.bd.com/pharmacysolutions/phaseal/">http://www.bd.com/pharmacysolutions/phaseal/</a>
ChemoClave Needle-free CSTD featuring Genie and Spiros	ICU Medical, Inc. 	Genie vial adapter has a Clave needle-free valve connector and an internal balloon that expands inside the vial to equate pressures; Needle-Free syringe adapter (Spiros) closed male luer; CH-74 protected filter vial-access device for vials not accommodated by Genie; Clave CSTD bag spike and bag spike CSTD with Clave additive port and dry spike; large selection of administration devices.	<a href="http://www.icumed.com/products/oncology/hazardous-drug-closed-systems-and-cstds/chemoclave-cstd.asp">http://www.icumed.com/products/oncology/hazardous-drug-closed-systems-and-cstds/chemoclave-cstd.asp</a>
ONGUARD Contained Medication System with Tevadaptor components	B. Braun Medical, Inc. 	Dual-filtered vial-access device for 20-mm closures; converter ring included for vials with 13-mm closures, Needle-Safe syringe adapter clicks onto vial adapter with no twisting; IV bag adaptor with secondary set or/spike port adaptor; Needle-safe IV push adaptor.	<a href="http://www.bbraunusa.com/products.html?acs=1&amp;prid=PRID00006969&amp;id=00020743040000000370">http://www.bbraunusa.com/products.html?acs=1&amp;prid=PRID00006969&amp;id=00020743040000000370</a>
EQUASHIELD – HD CSTD	Equashield Medical, Ltd. 	A <b>proprietary syringe unit</b> with 2 chambers, a liquid chamber and an air chamber, located at the end of the syringe piston is the containment device; a vial adapter attaches to the drug vial and the unique syringe clicks onto the vial adapter; shielded needles provide <b>needle-safe</b> protection; double-membrane connectors are used between the syringe unit and other components: IV bag spike adaptor, luer lock adaptor; luer lock connectors (male and female luer lock connections to luer lock ports).	<a href="http://www.equashield.com/">http://www.equashield.com/</a>

CSTD, closed system transfer device; HD, hazardous drug

validated high-pressure liquid chromatography (HPLC) with ultraviolet (UV) detector, HPLC with fluorescence detector, and inductively coupled plasma mass spectrometry techniques as appropriate.

Baseline results showed all of the surfaces sampled were contaminated with the marker drugs, including the surfaces of filled syringes and infusion bags. During the intervention phase, isolator surfaces were below limits of detection of the assays and the contamination measured on gloves, preparation mats, and the surface of infusion containers was markedly lower than during the baseline period. Sewell concluded that the use of the Tevadaptor device reduced both the frequency and amount of surface contamination by cytotoxic drugs when the marker drugs were used in similar quantities as during the baseline period.<sup>25</sup> The study also validated researcher concerns that the isolator is difficult to clean and any contamination left on the isolator surface may be transferred to the final product. Reducing the contamination on isolator surfaces reduced the contamination measured on gloves, preparation mats, and the final doses. The manufacturer sponsored the study.

Clark et al looked at contamination beyond the actual compounding BSC and the area immediately surrounding it, focusing on 5 areas adjacent to the pharmacy compounding area, including the dispensing counter, the half door and door handle, and areas in the infusion suite and offices areas.<sup>26</sup> Twelve samples were taken during each of the 3 snap-shot periods: baseline, 60 days after implementation of the CSTD (EquaShield, Equashield Medical) and cleaning, and 1 year later. The results from the first 2 sets show low levels of contamination with CP in about half of the positions in the 3 departments during both collection periods. The results from the final collection period show no contamination above the limits of detection with CP or FU in the pharmacy, infusion suite, or offices of the cancer center. The authors concluded that this independent study showed that “implementation of the [CSTDs] for preparing and administering chemotherapy eliminated surface contamination with cytotoxic agents at the ambulatory cancer chemotherapy infusion center.” However, many factors would impact surface contamination in a year-long period that could not be determined by a single snap shot of 12 wipe samples. For example, the amount of marker drugs (CP and FU) handled during the time preceding each sampling is not reported, nor is cleaning detailed during the year before the final sampling or in the period immediately preceding the

final sampling. These factors would significantly affect the amount of surface contamination.

## Visual Assessments

A strong visual assessment of the contamination generated using the traditional system compared with that generated with PhaSeal was published in 2003.<sup>32</sup> In a Carmel Pharma-sponsored study done by a member of the Scientific Advisory Board of Carmel Pharma, fluorescein was prepared both as a dry powder and as a 0.05% solution in saline in 100-mL vials for use as a surrogate agent. A series of manipulations were performed, with the products scanned with UV light and photographed using a digital camera with the room lights turned off to enhance the visualization of the fluorescence. Multiple manipulations were performed with 60-mL syringes. The traditional preparation of needles, syringes, and unprotected IV ports resulted in leakage demonstrated by visual fluorescence, whereas the PhaSeal system resulted in no visual leakage. Although no attempt was made to quantify the leakage, and visual fluorescence is not a sensitive method of assessment, this study presents a relatively easy and inexpensive evaluation of any device purporting to be a “closed system.”

Equashield contracted a fluorescein study with an outside analytical laboratory in 2009 to evaluate dry connections in the EquaShield, PhaSeal, and Tevadaptor/Onguard CSTDs.<sup>33</sup> This study used small vials of 0.05% fluorescein solution with multiple transfers of 2-, 5-, and 7-mL done with 20-mL syringes. Ten to 15 transfers were done with visual leakage assessed using UV light and photography. Administration simulation was done as 10 manipulations. This product-sponsored study resulted in only Equashield being residue-free during all manipulations. Both Tevadaptor/OnGuard, and PhaSeal showed leakage. Of PhaSeal systems, 40% showed leakage after a considerable number of manipulations (between 8 and 15 manipulations). As PhaSeal restricts the use of its system to 10 manipulations, most of these leaks would be outside the parameters of appropriate use. As with other visual assessments, no attempts are made to quantify the “leakage.”

An alternative visual method of assessing the integrity of devices marketed as closed systems was developed at a major university medical center by another member of the Scientific Advisory Board of Carmel Pharma.<sup>34</sup> A literal litmus test for examining leakage between 2 components of selected CSTD systems, the vial caps and the syringe adapters, was done by filling syringes with an unidentified low pH liquid and injecting

the fluid into vials attached to selected transfer devices. After aspirating back and disconnecting, the connections of each device were pressed against litmus paper to detect the presence of any fluid. Every component of each device was tested for 10 manipulations. In this test, visible leakage occurred outside of the components on the ICU Medical System Spiros and Clave connections; the B.Braun OnGuard System; and the Cardinal Health/Alaris System during all manipulations. No leakage was observed in any of the manipulations with the PhaSeal System. It should be noted that PhaSeal has the most recessed membranes of any of the available CSTDs, making the vial cap adaptor and the syringe adapter the most difficult to swab during aseptic processes. The recessed membranes also are difficult to access with the litmus paper, possibly reducing the wicking of liquid from the membranes.

This test presents another simple and inexpensive method for an initial assessment of CSTDs. It should be noted, however, that this system, as the fluorescein, provides no quantitative data to determine if any of these systems would meet a performance standard.

### **Visual Assessment for Vapor: To Filter or Not To Filter**

Several HDs are believed to vaporize at normal atmospheric conditions, thus by the terms of the CSTD definitions, closed systems must contain vapor. A unique system for creating a vapor was formulated at a major university medical center and the visual demonstration published by 2 members of Carmel Pharma's Pharmacy Advisory Board.<sup>35</sup> Developed by the University of Utah in 2007, titanium tetrachloride (TiCl<sub>4</sub>) provides a strong visual measure of containment. This protocol showed that all systems available at the time, with the exception of PhaSeal, failed a vapor challenge.

However, the appropriateness of TiCl<sub>4</sub> as a surrogate has been questioned. It has no properties similar to any of the available HDs and it is not a quantifiable chemical. It is difficult to use and has its own hazards. The demonstration itself shows a single attempt at containment by each of the devices. The authors noted that an independent laboratory reproduced the test, but they did not report the number of replications and conditions of the testing.

In direct rebuttal to the University of Utah study, B. Braun and Teva conducted 2 studies.<sup>36,37</sup> The Teva laboratory repeated the TiCl<sub>4</sub> smoke tests with Tevadaptor, and saw no smoke escaping from the system.<sup>36</sup> After a repeated injection of smoke, the venting channels of the system appeared to get blocked by a

white substance (TiO<sub>2</sub>) and no more smoke could be injected. When very high pressure was applied to try to force more smoke in the vial, in most cases, the blocked venting channels prevented further use of the system. On one occasion, smoke was seen to escape from the system. On visual inspection of this test sample, the Tevadaptor membrane appeared to be damaged by the hydrochloric acid that is formed in the reaction of TiCl<sub>4</sub> with moist air in combination with the pressure forcefully applied to the system. B.Braun compared physical and chemical characteristics of actual HDs to those of TiCl<sub>4</sub> in a contracted report and demonstrated the effectiveness of the Tevadaptor filters with etoposide, carboplatin, doxorubicin, and CP in tests conducted by an independent laboratory.<sup>37</sup>

Equashield tested its device against PhaSeal and the ICU Genie/Clave with TiCl<sub>4</sub> in a paid laboratory protocol.<sup>38</sup> ICU's product did not contain the vapor. The Equashield system appeared as effective as PhaSeal in visually containing the vapor.

### **Surrogate Interventions: Technetium**

Several quantitative studies have been done with radioactive technetium. Many of the CSTD systems contain this surrogate because it is a true particle not a vapor. Radiation, however, has its own safety and exposure limits, and manipulating large volumes of up to 50 mL in 60-mL syringes using multiple transfers may exceed these limits. Technetium also has a short half-life, so activities and measurements must be taken immediately. Systems requiring more time would show smaller volumes transferred. These issues present an argument against using radioactive technetium as a useful surrogate.

A study by Nygren et al investigated the difference in airborne emission and surface leakage with the traditional open technique and the PhaSeal system.<sup>17</sup> Platinum was used for the airborne emission tracer, with air samples taken in the preparation and administration areas. The radioisotope technetium 99m was used to measure spills and leakage on surfaces by measuring radiation on gloves and benchtops. Ten nurses were the test participants and each nurse prepared and administered 6 doses in the open system and the closed system via IV push. There was a large variation in leakage among the nurses using the traditional system for preparation and administration. The closed system resulted in a decrease in measured radiation of 3 to 4 orders of magnitude. Airborne emission was difficult to measure but was less than surface leakage when the PhaSeal system was put into use. However,

the difference in airborne emission between the techniques was small and not statistically significant. The authors concluded that when using the traditional technique, even skilled nurses encounter large spills and have difficulty avoiding leakage. In contrast, inexperienced nurses could, after a short introduction, use the PhaSeal system with only minor spills.

The small number of participants and the fact that doses of only 6-mL volumes in small syringes were used weaken this study. It is surprising that there was significant leakage with such small syringes and volumes. Many HD doses are much larger and require larger volumes (60-mL syringes), creating significantly more risks for leakage and spills, so this simulation is limited in its scope.

In another study, Nygren et al tested the Tevadaptor for spill and leakage during drug preparation using a radioactive technetium surrogate as in previous studies.<sup>18,29</sup> In the test procedure, 6 mL was withdrawn from a 10-mL vial of technetium surrogate, using a disposable syringe and the Tevadaptor. The syringe was then disconnected from the vial and connected to an infusion bag using a connection device for the Tevadaptor and the content was injected into the IV bag. After the injection, the syringe was disconnected from the infusion bag. Bench covers were used to capture any radioactive surrogate leaked during the process. The bench cover and the gloves were collected after each preparation and measured for radioactivity, which would indicate leakage.

The test results showed the spill was less than 100 nL for all 75 preparations and was less than 1 nL for 70 of the preparations. This is comparable with the previous study of PhaSeal.<sup>17</sup> The test shows that the Tevadaptor drug-handling system has similar performance as drug-handling systems regarded as closed systems.

French researchers used a radioactive solution of sodium pertechnetate per the Nygren study<sup>29</sup> to evaluate multiple CSTDs using several criteria.<sup>27</sup> Four devices available in the United States and France were compared: PhaSeal with expansion chamber; Tevadaptor with filter; Clave with filter and Spiros; and Smart-site with filter and Texium. Evaluation criteria included transfer performance of the radioactive solution from one vial to another measuring leakage, contamination, dead space, residual volume, and efficiency. No details of training on use of the systems was included, but PhaSeal is noted not to be intuitive to use and several of the areas where PhaSeal scored low may be due to the fact that the operator was not familiar with the need to accommodate air/fluid transfers by drawing air into the

syringe before transfer. Because the other CSTDs compared are filter systems, they are used more easily with no training. As with all test systems using radioactive solutions, the volumes transferred in this study were quite small (only 2-mL syringes were used), but small syringes and volumes are not true tests of HD transfers. Additionally, the half-life of this agent is quite short, so the time required performing a task negatively affects the perceived efficiency. Although PhaSeal scored high in containment, the weighted rating for that function was less than for efficiency, where it scored badly. Efficiency and operator ease-of-use scores made PhaSeal the least acceptable in this study.

A US group also used a liquid radioactive technetium isotope as a surrogate to evaluate several systems: ChemoClave with Genie and Spiros; OnGuard with Tevadaptor components; and PhaSeal.<sup>28</sup> Using a variation of the test method proposed by Nygren,<sup>29</sup> investigators used wipes to sample for surrogate leakage on the CSTD connections. Nine manufacturer-trained oncology pharmacists and pharmacy technicians each manipulated one system set of 15 preparations. Syringe and vial adapters were connected, and 6 mL of the test solution was drawn into the syringe; then the vials and syringe adapters were disconnected, and a 70% isopropyl alcohol prep pad was wiped on the usual entry points of the syringe and paired spiked vial adapters. Because the OnGuard syringe and PhaSeal vial adapters have an outer rim that projects from and surrounds the points of vial entry, the prep pads were inserted into these enclosed spaces and turned 720 degrees twice. As in the Nygren study,<sup>29</sup> the researchers controlled for the time lapse from collection to performance of measurements to correct for degradation of the surrogate. Comparisons among participants and devices were conducted via analysis of variance (ANOVA) on 135 wipe samples per system (15 wipe samples per each of 9 participants).

ANOVA results indicated significant differences among devices in leakage of the test solution, with the PhaSeal device having the lowest geometric mean leakage (0.1 nL; 95% confidence interval [CI], 0-0.2 nL), followed by the OnGuard (1.5 nL; 95% CI, 1.1-1.9 nL) and ChemoClave (35.6 nL; 95% CI, 29.1-43.6 nL) devices. Overall, the reported leak volumes were small. The authors noted that the clinical implications of the leakage levels detected are unknown and that there are no standard amounts or limits above which clinically significant complications, such as secondary malignancies, are known to arise.

## Other Factors

A Canadian medical center compared 3 CSTD systems—PhaSeal, OnGuard, and ChemoClave (components not reported)—to identify any negative, user-related issues.<sup>39</sup> Using a prospective, within-subject study design, in which each participant completed a task using each system in counterbalanced order. Mixing and administration were done with a visual fluorescein marker. Quantitative data was collected about error and success rates using a checklist, along with qualitative data about participant's experiences using a questionnaire, photos, and video. Twelve nurses and 12 pharmacy assistants participated in the study. PhaSeal required the most amount of time to complete the tasks overall. PhaSeal and OnGuard showed comparable effectiveness based on the amount of fluorescein detected on critical sites. PhaSeal generally scored lower on user preference and user comments about ease of training. ChemoClave required the least amount of time to complete the tasks for both pharmacy assistants and nurses; however, it appeared to be the least effective based on the amount of fluorescein detected on critical sites. The author concludes that no CSTD system is perfect; all systems showed varying degrees of usability challenges. Each system requires proper staff training, and reliance on user intuitiveness is not enough.

## Conclusion

There are a number of FDA-cleared Class II medical devices that are marketed as “CSTDs” or other “closed” or “contained” systems, and they differ in how they attempt to meet the NIOSH definition of a CSTD. A variety of surrogates and test systems have been used to evaluate these devices for their effectiveness in reducing surface contamination generated in the handling of HDs, thereby reducing occupational exposure to these harmful agents. Results from the reviewed intervention studies indicate that closed systems provide better protection from HD exposure than traditional techniques. This is especially true with administration tasks. In clinical settings, studies done predominantly with PhaSeal, provided varying results. Whereas in some studies, environmental monitoring showed little or no contamination, others showed that contamination did occur, although at lower levels. Use of a closed system is shown to reduce leakage of HDs during normal drug preparation and administration activities, compared with the use of needles and syringes, but these devices do not completely eliminate exposure. Some of the factors that influence

exposure may include user technique, BSC function, and unpredictable occurrences such as breakage or spills. Because leakage did occur in several studies, the products cannot be considered completely “closed systems.” Thus, closed systems should be considered adjuncts to, and not substitutes for, other safe handling precautions.

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